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Presentation and Outcomes with Clinically Apparent Interferon Beta Hepatotoxicity

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Abstract

AIMS—The aim of this study was to describe the presenting features and outcomes of consecutive patients with liver injury attributed to interferon beta.

Methods—The presenting features of 8 subjects with clinically apparent liver injury attributed to interferon beta enrolled in the U.S. Drug-Induced Liver Injury Network (DILIN) prospective registry between 2004 and 2010 were reviewed and compared to 11 published reports of symptomatic hepatotoxicity.

Results—All 8 of the DILIN patients were women, 75% were Caucasian and the mean age was 49 years. Most subjects presented with an acute hepatocellular injury pattern and mean serum alanine aminotransferase (ALT) levels were 725 ± 593 U/L. The median duration of interferon beta use before injury onset was 462 days, and 4 patients had been treated for more than a year. No patient had detectable antinuclear or smooth muscle antibodies. One patient died of acute liver failure and the remaining patients usually recovered within 2 to 3 months. Causality assessment scored 3 cases as definite, 3 highly likely, 1 probable and 1 possible. Eleven additional published cases were all women, mean age was 40 years, mean ALT at onset 840 U/L, and 7 (63%) had autoantibodies. Liver histology in 3 cases from DILIN and 9 from the literature commented upon centri-lobular (zone 3) necrosis and infiltrates with lymphocytes and plasma cells.

Conclusions—Interferon beta hepatotoxicity occurs mostly in women and has a variable, but often prolonged time to onset. Most patients have self-limited acute hepatocellular liver injury but several have required liver transplantation or died of acute liver failure. Liver histology available in 3 cases demonstrated zone 3 necrosis and autoimmune features suggestive of an immunologic basis to this adverse drug reaction.

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Keywords

Multiple sclerosis; biologic response modifiers; drug-induced liver injury; acute liver; failure; liver biopsy

Introduction

An estimated 200,000 Americans have multiple sclerosis (MS) with an increased incidence and earlier age of onset consistently reported in women compared to men (1). Although the pathogenesis of MS remains unknown, the most widely accepted theory is that MS begins as an autoimmune inflammatory disorder of the myelin sheath (2). As a result of its presumed inflammatory pathogenesis, several immunomodulatory therapies are currently used to treat patients with intermittently relapsing and progressive MS (3). Since 1993, three forms of interferon beta have been approved for use in patients with relapsing or progressive MS and many patients are currently treated with these injectable biological peptides for weeks, months or even years (3,4). Interferon beta is a potent systemic cytokine and has frequent side effects including fatigue, myelotoxicity, and neurotoxicity that mandate careful clinical and laboratory monitoring (5). In reviews of clinical trials, observational studies, and post-marketing reports in which monitoring was performed, 37 to 64% of treated patients developed evidence of liver injury as shown by elevations in serum alanine (ALT) or aspartate (AST) aminotransferase levels (5–7). In the majority of patients the serum ALT elevations were mild and transient and often fell into the normal range even with continued treatment or with transient dose reduction or interruption. However, a proportion of patients developed symptoms or jaundice and in some cases severe liver injury progressed to acute liver failure that led to emergency liver transplantation (8,9). Reliable estimates of the incidence of DILI in a patient population or attributed to a specific agent are notoriously difficult to garner due to the general under-reporting of adverse drug reactions to regulatory agencies (10).

Because most instances of drug induced liver injury (DILI) are idiosyncratic and independent of the dose, duration, or indication of the drug, it is not possible to predict or prevent them from occurring. Furthermore, there are no objective confirmatory diagnostic tests for DILI; making it a difficult diagnosis which requires the exclusion of other more common causes of liver injury (10,11). A diagnosis of DILI can be made with greater confidence if the clinical features match the “signature” of liver injury described in case reports or case series in the literature. In most instances, however, DILI is a diagnosis of exclusion.

The Drug Induced Liver Injury Network (DILIN) was created in 2003 to improve the understanding of the epidemiology, mechanisms, risk factors, and natural history of DILI in the United States. As of December, 2012, more than 1,100 patients have been enrolled into the DILIN prospective registry study wherein a detailed medical history, laboratory evaluation, and formal causality assessment are undertaken (1213). The current study was undertaken to better characterize the presenting features, risk factors, and outcomes with DILI attributed to interferon beta based upon patients enrolled in DILIN between 2004 and 2010 who had completed follow up and undergone formal causality assessment. The features of these cases were also compared to case reports and series of interferon beta hepatotoxicity reported in the literature.

Methods

The Drug Induced Liver Injury Network (DILIN)

DILIN is an NIH-funded multicenter prospective observational cohort study that enrolls well-characterized patients with suspected DILI into a centralized database for clinical and mechanistic studies (12,13). All subjects > 2 years of age who meet minimal laboratory criteria of liver injury due to any known prescription or over-the-counter drug or herbal and dietary supplement (other than acetaminophen) are eligible for enrollment if seen within 6 months of onset. Laboratory inclusion criteria are an AST or ALT > 5 times the upper limit of normal (ULN) (or pretreatment baseline if abnormal) on 2 consecutive occasions, an alkaline phosphatase > 2×ULN (or pretreatment baseline if abnormal) on 2 consecutive occasions or a total serum bilirubin > 2.5 mg/dl or an INR > 1.5 with any elevation in ALT, AST, or alkaline phosphatase. All participants undergo an extensive review of their medical history, evaluation for more common causes of liver injury such as hepatitis A, B, C, Epstein-Barr virus hepatitis, cytomegalovirus hepatitis, autoimmune hepatitis, pancreaticobiliary disease, and alcohol. In addition, extensive medication use history is collected and all subjects are asked to return for a 6 month follow-up visit. The prospectively acquired data are then reviewed by an expert group of hepatologists through a formal causality assessment process previously described (14). Each suspect drug is assessed on a scale of 1 (definite or > 95% likelihood), 2 (highly likely or 75–95% likelihood), 3 (probable or 50–75% likelihood), 4 (possible or 25–50% likelihood) or 5 (unlikely or < 25% likelihood). The severity of the DILI episode is also scaled from 1 (serum enzyme elevations without jaundice), 2 (serum enzyme elevations with jaundice: total bilirubin > 2.5 mg/dL), 3 (liver injury with jaundice leading to hospitalization or prolongation of existing hospitalization), 4 (evidence of hepatic failure: INR > 1.5, ascites, encephalopathy) to 5 (Emergency liver transplantation or death). Cases were categorized on the basis of the R ratio at the time of onset of injury as either hepatocellular (R >5), cholestatic (R<2) or mixed (R = 2–5); the R value representing the ratio of the ALT to alkaline phosphatase (Alk P), both expressed in multiples of the upper limit of normal.

All subjects gave written informed consent, and all details of the study were approved by a local Institutional Review Board (IRB) and by the central Data Safety and Monitoring Board (DSMB) appointed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) specifically for this study.

Liver histology

Enrolled patients were not required to have a liver biopsy, but if obtained as a part of clinical care, liver biopsy slides were reviewed centrally by a single, expert hepatopathologist (DEK). The pattern of injury and histological features were assessed in a blinded, systematic manner.

Literature review

In July 2011, a MEDLINE search was undertaken to identify published cases of liver injury due to interferon beta. The search terms interferon, interferon beta, hepatotoxicity, hepatitis, acute liver failure, and multiple sclerosis were used. One of the authors (RJF) then reviewed the identified references and summarized the presenting features and outcomes of reported patients.

Statistics

Summary statistics were employed including calculation of means, standard deviations and proportions. For values that were not normally distributed medians or means of logarithmically transformation values were used.

Results

Between 2004 and July 2010, 784 patients were enrolled into the DILIN cohort study and completed 6 months of follow up and full adjudication of causality. Eight cases (1%) were attributed to interferon beta. All of the interferon beta cases occurred in women, 75% were non-Hispanic whites and the mean age was 49 years (range 33 to 64 years) (Table 1). All 8 patients had multiple sclerosis and were being managed by a neurologist. All three formulations of interferon beta were represented (3 due to Interferon beta 1a (Avonex) given intramuscularly; 4 due to Interferon beta-1a (Rebif) given subcutaneously; 1 due to Interferon beta 1b (Betaseron), given subcutaneously) and the dose at the time of injury onset ranged widely from 30 to 144 ug per week. Latency (i.e the time from initiation of therapy to DILI onset) also varied greatly from 101 days to 12.8 years with a median of 462 days (1.3 years). At presentation, 6 subjects had a hepatocellular liver injury pattern with a mean R ratio of 13.6, whereas the remaining two had a mixed pattern (R values 3.2 and 4.3). Five patients had symptoms of liver injury and 4 were clinically jaundiced. Following discontinuation of interferon beta, 5 subjects improved and no longer had evidence of liver injury at 6 months of follow-up while 2 had persistent biochemical abnormalities and one died. The severity of injury was graded as mild (1+) in 4 patients, moderate (2+) in 2, moderate requiring hospitalization (3+) in 1 and fatal (5+) in 1.

Causality assessment scored 3 cases as definite, 3 as highly likely, one as probable and 1 possible. Liver histopathology was available for review from 4 patients and is described in the individual case vignettes. Common findings were centrilobular (zone 3) necrosis and moderate chronic inflammatory infiltrates with lymphocytes, eosinophils and plasma cells. Clinical case reports of 3 patients are given below and those of the remaining 5 patients are provided in the Supplementary Materials. Testing for IgM antibody to hepatitis E virus (anti-HEV) was negative in all 8 patients.

Patient #8

A 33 year old African American woman with MS presented with a 1 week history of fatigue, nausea, and jaundice. She had been treated with interferon beta-1a in a dose of 44 mcg intramuscularly, 3 times a week for 9 months. The last dose was given 3 days before presentation. She was severely obese with a body mass index (BMI) of 47.8 kg/m^2 but had no history of diabetes or known liver disease. She denied drug allergies and was on no concomitant medications or over the counter products. She did not smoke or drink alcohol. Physical exam at the time of hospitalization showed scleral icterus but no fever, rash or hepatosplenomegaly. Initial laboratory tests revealed ALT 1,901 U/L, AST 1,157 U/L, Alk P 224 U/L, total bilirubin 4.5 mg/dL, and INR 1.0. Viral hepatitis and autoimmune serologies were negative, and an endoscopic retrograde cholangiopancreatogram (ERCP) was normal. She was discharged but rehospitalized shortly thereafter with persistent jaundice. Magnetic resonance imaging revealed diffuse hepatic signal abnormality suggestive of acute hepatic inflammatory changes. A liver biopsy 30 days after onset revealed zone 3 necrosis and scattered areas of bridging and multiacinar necrosis (Figure 1). Plasma cells were prominent particularly in the areas of necrosis and there was sparse inflammation along the interface between the necrotic and viable areas. There were foci of lobular inflammation with hepatocyte rosette formation and only mild inflammation in the portal areas. Her condition deteriorated with worsening jaundice (total bilirubin rising to 25 mg/dL), coagulopathy (INR 2.2), and hepatic decompensation with ascites and altered mental status about 6 weeks following presentation (Figure 1). Corticosteroids were started 10 weeks after DILI onset but she did not improve and developed sepsis and multi-organ failure and died 84 days after initial presentation. An autopsy showed massive hepatic necrosis and collapse with areas of nodular regeneration. ***Comment:*** This patient presented

with a severe acute hepatitis with jaundice 9 months after starting interferon beta. In the absence of a competing diagnosis or concomitant medications, this presentation was strongly suggestive of DILI due to this agent. The DILIN adjudication process rated the case as definite and the DILIN severity score was 5 since she died of liver failure.

Patient #5

A 59 year old non-Hispanic white woman was started on interferon beta-1a at a dose of 44 mcg subcutaneously, three times a week for worsening of longstanding MS. She had received interferon beta-1b previously for 3 years which was stopped for a year due to disease stabilization. Four years after interferon beta-1a (44 ug three times a week) was resumed, she was found to have elevation of liver enzymes in the course of routine monitoring associated with dark urine but no additional symptoms. She had no allergies and did not smoke or drink alcohol. Other medical conditions included chronic obstructive pulmonary disease, hyperlipidemia, chronic urinary tract infections, and depression for which she was chronically (>1 year) taking. ezetimibe-simvastatin, nitrofurantoin, estrogens and olanzapine which she continued to take. A physical exam at the time of presentation was unremarkable. Laboratory test results included serum ALT 1,225 U/L, AST 716 U/L, Alk P 220 U/L and total bilirubin 2.8 mg/dL. Viral hepatitis and autoimmune serological testing was negative. Liver ultrasound was normal. Due to concern for hepatotoxicity, both interferon beta and ezetimibe-simvastatin were discontinued with improvement but not complete normalization in her serum aminotransferase levels. A liver biopsy was not performed. The asymptomatic liver enzyme abnormalities persisted 6 months after DILI onset with a serum ALT 100 U/L, AST 63 U/L, and Alk P 98 U/L consistent with chronic injury but she was then lost to follow-up (Figure 2). ***Comment:*** This patient presented with asymptomatic liver enzyme elevations that improved but remained persistently elevated during follow-up. Competing etiologies of liver injury were ruled out. Interferon beta was a suspect drug as well as ezetimibe-simvastatin. The DILIN adjudication process rated the likelihood of interferon beta as the cause of DILI as highly likely and that of ezetimibe-simvastatin as possible. The DILIN severity score was 2+ based on liver enzyme elevation with hyperbilirubinemia.

Patient #7

A 64 year old non-Hispanic white woman presented with symptomatic hepatitis 5 days after starting oxaprozin for arthritis. The patient had been on interferon beta 1a at a dose of 30 mcg intramuscularly once weekly for MS for 13 years. Other medical conditions included hypertension, hyperlipidemia and bipolar disorder for which she had been treated with hydrochlorothiazide, lisinopril, simvastatin, clonazepam, and tizanidine for several years. She also took polyethylene glycol for constipation periodically but no other over-the-counter or herbal products. She reported that codeine caused nausea but had no other drug allergies, no personal or family history of liver disease and did not drink alcohol or smoke. In the two weeks before presentation, she reported having muscle aches and chills. Examination showed a diffuse, moderate-to-severe erythematous rash with facial swelling. Initial laboratory tests showed an ALT 477 U/L, AST 713 U/L, Alk P 349 U/L, total bilirubin 0.6 mg/dL and normal INR. Of note, she had mild eosinophilia at presentation of 6.9% which later peaked at 14.5%. Viral hepatitis and autoimmune serologies were negative as was liver imaging. Both oxaprozin and interferon beta were discontinued and she received a 2 week course of corticosteroids for the liver injury and immunoallergic features. Her liver enzymes initially improved but then further increased two weeks later (ALT 591 U/L, Alk P 258 U/L). A liver biopsy performed 24 days after DILI onset showed zone 3 necrosis and focal bridging necrosis (Figure 3). A mild infiltrate of plasma cells and lymphocytes with scattered eosinophils were present in zone 3. Early portacentral bridging fibrosis was seen. Without further intervention, her serum aminotransferase levels began to improve and were

normal within 2 months of stopping the medications and remained normal thereafter. ***Comment:*** This patient presented with symptomatic immunoallergic hepatitis that led to a 3-day hospitalization that improved with supportive care and a short-course of corticosteroids. Her liver enzymes normalized within two months and the liver biopsy was consistent with a recent toxic liver injury. The DILIN adjudication process rated this case overall as highly likely DILI with oxaprozin assigned a highly likely causality score due to its strong temporal relationship with her illness and published reports of a similar rapid onset liver injury with immunoallergic features after use of this agent (15). Interferon beta was given a causality score of possible due to the prolonged duration of use without evidence of hepatotoxicity. The DILIN severity score was 3+ (jaundice and hospitalization).

Review of the literature

A total of 11 unique patients with clinically apparent hepatotoxicity attributed to interferon beta were identified in the published literature (Table 2) (9,16–24). All patients had MS and all were women. The mean age at liver injury onset was 40 years (range 24 to 59 years). Applying the DILIN scale for severity, 3 cases (27%) were scored as mild, 3 (27%) moderate, 2 (18%) moderate requiring hospitalization and 3 (27%) severe or fatal. Interestingly, the time to DILI onset was highly variable with a range of 14 to 1825 and a mean of 386 days. Serum ALT and Alk P levels were not available from all cases, but an initial enzyme pattern indicating acute hepatocellular injury was present in 5 instances (45%) and at least 6 (54%) subjects had an elevated bilirubin level at presentation. Two patients were able to continue therapy with improvement, but one patient eventually experienced a relapse in hepatitis that worsened over time. In addition, another patient who had prior hepatotoxicity with interferon beta developed severe recurrent liver injury upon rechallenge (16). Liver histology in 9 cases showed zone 3 necrosis of varying severity in most and autoimmune like findings in two. Of note, plasma cells and zone 3 necrosis were prominent in the 3 DILIN cases that were biopsied. At least 7 patients had detectable autoantibodies and 5 of these improved with immunosuppressive therapy. Overall, 3 patients required liver transplantation although it was later reported that one patient had received nefazodone as well which raised some doubt about the role of interferon beta (9). None of the case reports reported a formal causality assessment score.

Discussion

Interferon beta is considered a first line of therapy for MS in those with relapsing and progressive symptoms (3,4). Clinical experts suggest that serum aminotransferase levels be monitored with testing every 3 months during the first year of therapy and thereafter if there are unexplained symptoms of possible liver injury such as fever, malaise, abdominal pain, or jaundice in accordance with the product package inserts (25). Hepatic abnormalities have been well-documented in MS patients treated with all of the available forms of interferon beta both in clinical trials and post-marketing surveillance studies (4–9). These abnormalities are typically mild serum aminotransferase elevations which can resolve even with continued therapy or with dose reduction. In addition, the majority of these abnormalities occur within the first 6 months of starting treatment and less than 1% of treated patients require drug discontinuation due to hepatotoxicity (4–9). In addition, serum aminotransferase elevations have been observed in up to 40% of patients treated for a year or more in clinical practice and appear to be related to the cumulative dose administered (26). An analysis of post-marketing surveillance data suggested that the incidence of symptomatic hepatotoxicity with interferon beta averages 1 per 2300 treated-patients or 1 per 4,000 patient-years of use, but detailed information regarding potential risk factors for clinically significant hepatotoxicity have not been well-defined (5).

The current review of the DILIN database identified 8 subjects (1%) with clinically significant liver injury attributed to interferon beta over a 6 year period during which 784 patients were enrolled into the prospective registry. All patients underwent a complete medical evaluation, competing causes of liver injury were excluded and all patients were followed for at least 6 months to further define the outcome of the liver injury. Of note, there is likely an underreporting of DILI cases to the DILIN clinical sites as there is to regulatory agencies and the incidence of interferon beta hepatoxicity can not be reliably inferred from our study. Six of the 8 patients in our series presented with an acute hepatocellular liver injury pattern and 3 had ALT levels that rose above 1000 U/L The majority of patients had resolution of their liver injury within 6 months of drug discontinuation but two patients demonstrated evidence of persistent liver injury during follow-up. Unfortunately, subject # 8 developed progressive liver injury culminating in death at 3 months after initial presentation and at least 3 other case reports of severe hepatotoxicity leading to liver transplantation have been identified (Table 2). The time to develop hepatotoxicity and the dose of interferon beta at DILI onset were highly variable in our series (Table 1) as well as in the published literature (Table 2). Four of the DILIN patients had been receiving interferon beta for more than a year and subject #7 had been on interferon beta for over 13 years. The dose of interferon beta at the time of DILI onset was typical of doses reported in other subjects with hepatotoxicity. Causality scores were definite or very likely in 75% of the DILIN cases.

All 8 of our patients were women, 75% non-Hispanic white and the mean age was 49 years. These demographic features are consistent with the overall epidemiology of patients with MS, which is known to largely afflict middle aged individuals of all races and ethnicities with a similar frequency. However, the 100% female predominance in this series as well as other published case reports of severe hepatotoxicity (Table 2) was higher than expected since only 75 % of cases of MS occur in women although the proportion of female cases appears to be increasing over time (27). Furthermore, during the clinical trials of these agents a higher frequency and severity of serum aminotransferase levels were reported in men compared to women (57). However, an analysis of post-marketing surveillance data of over 70,000 patients treated with interferon beta 1a also demonstrated that all except one of the 30 patients with severe hepatic dysfunction were women (5).

Women may be more susceptible to severe hepatotoxicity from interferon beta and other drugs due, in part, to their lower mean body weight and generally better medication adherence compared to men (28). Previous analyses of the first 300 patients enrolled in the DILIN database and those enrolled in other DILI registries have not demonstrated an over-representation of women compared to men for DILI of all causes (1229). However, there appears to be an overrepresentation of female patients (71%) amongst those with acute liver failure due to severe idiosyncratic drug-induced liver injury (30). Women may be more susceptible to severe DILI due to impaired liver regeneration and poorer clearance of the suspect medication from the body (11). In addition, the lower average body weight of women may predispose them to a greater susceptibility to DILI. Finally, the intrinsic immunostimulatory properties of interferon beta coupled with the fact that women are known to be more susceptible to various autoimmune diseases including autoimmune hepatitis and primary biliary cirrhosis may, in part, account for our observations. Of note, the mean BMI of the 8 women in the DILIN registry with interferon beta hepatotoxicity was not low and in fact 37% met criteria for obesity consistent with the expected prevalence of obesity in the general US population.

The risk factors for and mechanism(s) of interferon beta hepatotoxicity are largely unknown. Interferon beta is a normal human cytokine that is endogenously produced by fibroblasts and epithelial cells in response to viral and antigenic stimuli. Interferon beta is structurally distinct from interferon alpha but they share the same cell surface receptors, although they

have somewhat different intracellular actions resulting from activation of separate signaling pathways. The 3 commercially available interferon beta products are recombinant, parenterally administered polypeptides. Interferon beta-1a has direct effects on hepatocytes acting through cell surface receptors and leading to changes in gene expression and protein synthesis and hepatocyte ultrastructure (31). Interferon beta can depress the activity of inducible and constitutive cytochrome P-450 isoenzymes that may alter the metabolism of other drugs (3233).

Interferon alpha which is used to treat patients with chronic viral hepatitis leads to worsening serum aminotransferase levels in a small proportion of patients that usually improves with drug discontinuation. Isolated case reports of an autoimmune-like hepatitis have been reported in patients with chronic hepatitis C treated with interferon alpha that, in some presumably represents an exacerbation of pre-existing autoimmune liver disease while in others it may represent de novo development or triggering of autoimmune hepatitis (34). In this case series, liver histology demonstrated centrilobular necrosis and in 3 cases sparse inflammatory cell infiltrates containing lymphocytes and plasma cells, changes that are reminiscent of spontaneous autoimmune hepatitis (3536). While none of our 8 patients had detectable autoantibodies or hypergammaglobulinemia at presentation, 7 (63%) of 11 patients in the literature were reported to have autoantibodies (Table 2). Typical autoantibodies such as antinuclear and smooth muscle antibodies are, however, common in persons with MS (3738) and not uncommon in unaffected asymptomatic adults in the normal U.S. population (39). The patient with the most severe liver injury in our series (#8) had marked necrosis with autoimmune features on biopsy but died of progressive liver failure despite the use of corticosteroids.

In summary, 8 of 783 patients (1%) with drug induced liver injury enrolled in a prospective registry study in the United States had liver injury attributed to use of interferon beta for MS. Prominent clinical features were that all patients were women and that the time to onset of injury was prolonged and highly variable, ranging from 100 days to several years. The hepatic injury was typically hepatocellular and liver histology indicated centrilobular necrosis and chronic inflammatory infiltrates suggestive of an immunologic mechanism of injury. Patients with MS who are to receive interferon beta should e tested for evidence of liver injury before starting treatment and be monitored for evidence of liver injury with particular attention to the development of clinical symptoms during treatment. The prolonged and highly variable latency in the DILIN cases reported here as well as previously published reports highlight the need for continuous vigilance and lab monitoring when using this agent. The cause of liver injury during interferon beta therapy deserves further analysis focusing particularly on genetic and immunologic features.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The website https://dilin.dcri.duke.edu/publications-1 provides a complete listing of DILIN funding sources, DILIN sites, Investigators, Co-Investigators, Coordinators, and Staff.

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Abbreviations used

ALT	alanine aminotransferase
AST	aspartate aminotransferase
Alk P	alkaline phosphatase
DILI	drug-induced liver injury
DILIN	Drug-Induced Liver Injury Network
IFN	interferon
MS	multiple sclerosis
ULN	upper limit of the normal range

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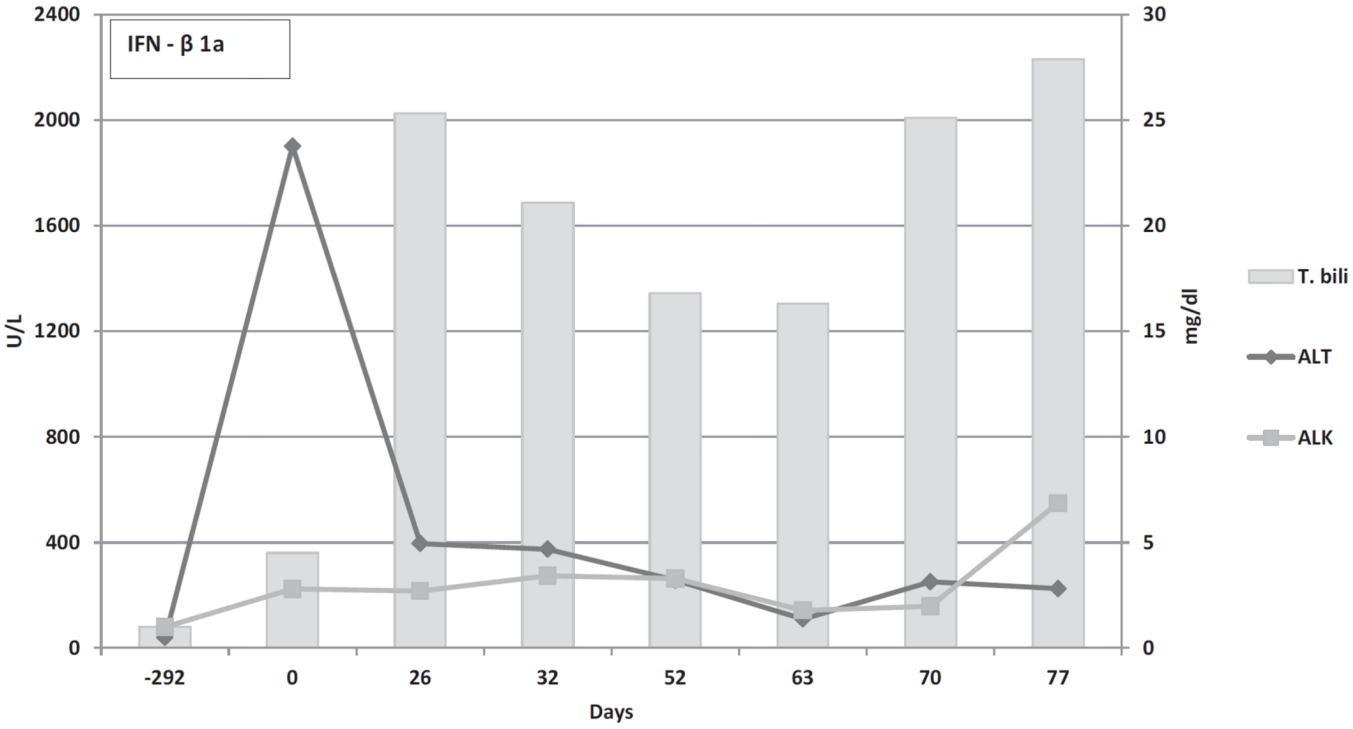

Figure 1. Serial laboratory values in a 33 year old African American woman with MS treated with interferon beta 1a

At month 9, she presented with jaundice and marked elevations in serum aminotransferase levels (Case #8). Autoantibodies were not detectable. A transjugular liver biopsy on day 30 showed severe zone 3 necrosis with areas of bridging and multiacinar necrosis. Despite use of corticosteroids, she died of liver failure 3 months after presentation. (The ULN at the DILIN site are as follows: ALT= 35 IU/L, Alk phos=130 IU/l, total bilirubin =1.2 mg/dl)

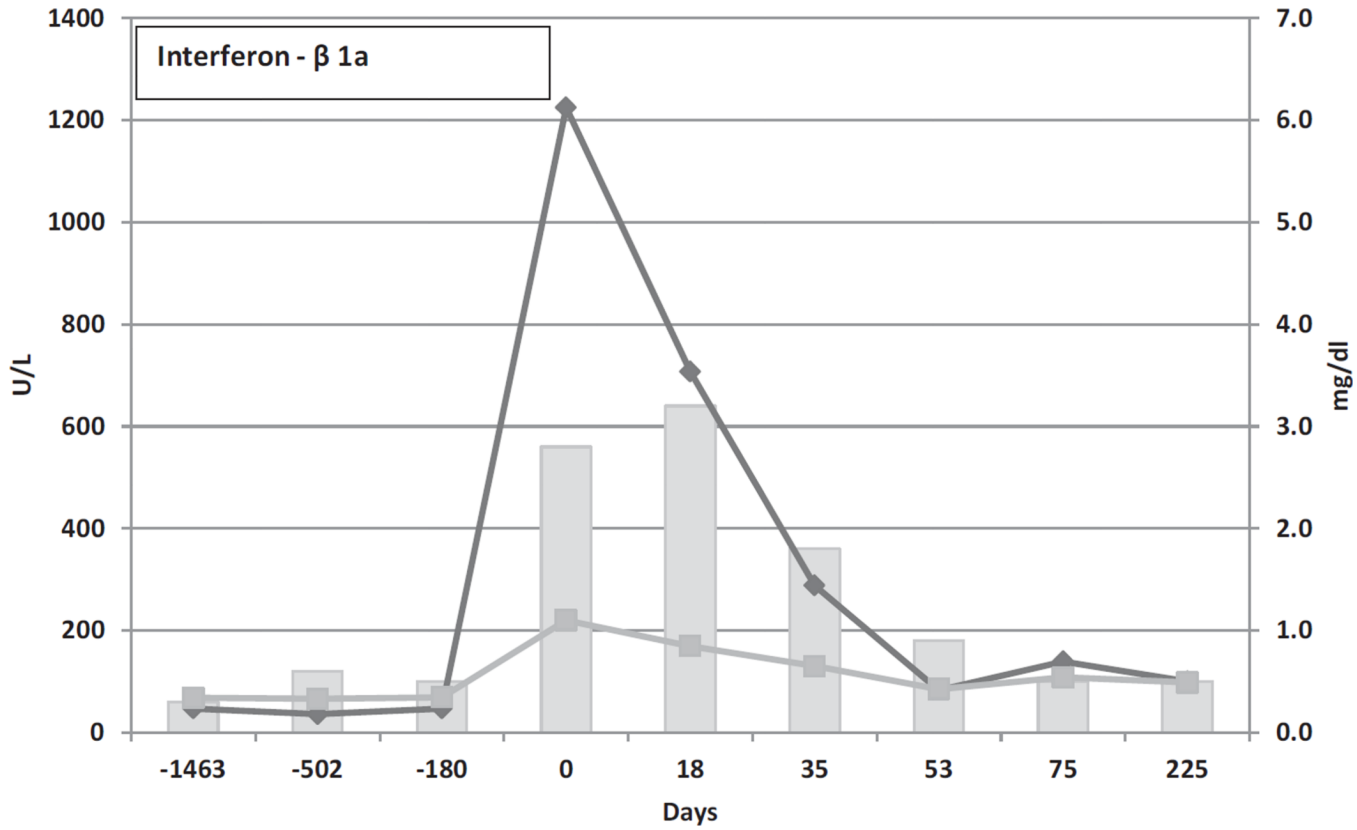

Figure 2. Serial laboratory values in a 59 year old non-Hispanic white woman with relapsing MS

She developed elevations in serum enzymes four years after a second course of interferon beta 1a at which point serum ALT was 1,225 U/L, Alk P 220 U/L, and total bilirubin 2.8 mg/d (case #5). Both interferon beta and ezetimibe-simvastatin were discontinued and liver biochemistries improved but remained mildly elevated when tested 6 months later. (The ULN at the DILIN site are as follows: ALT= 35 IU/L, Alk phos=130 IU/l, total bilirubin =1.2 mg/dl)

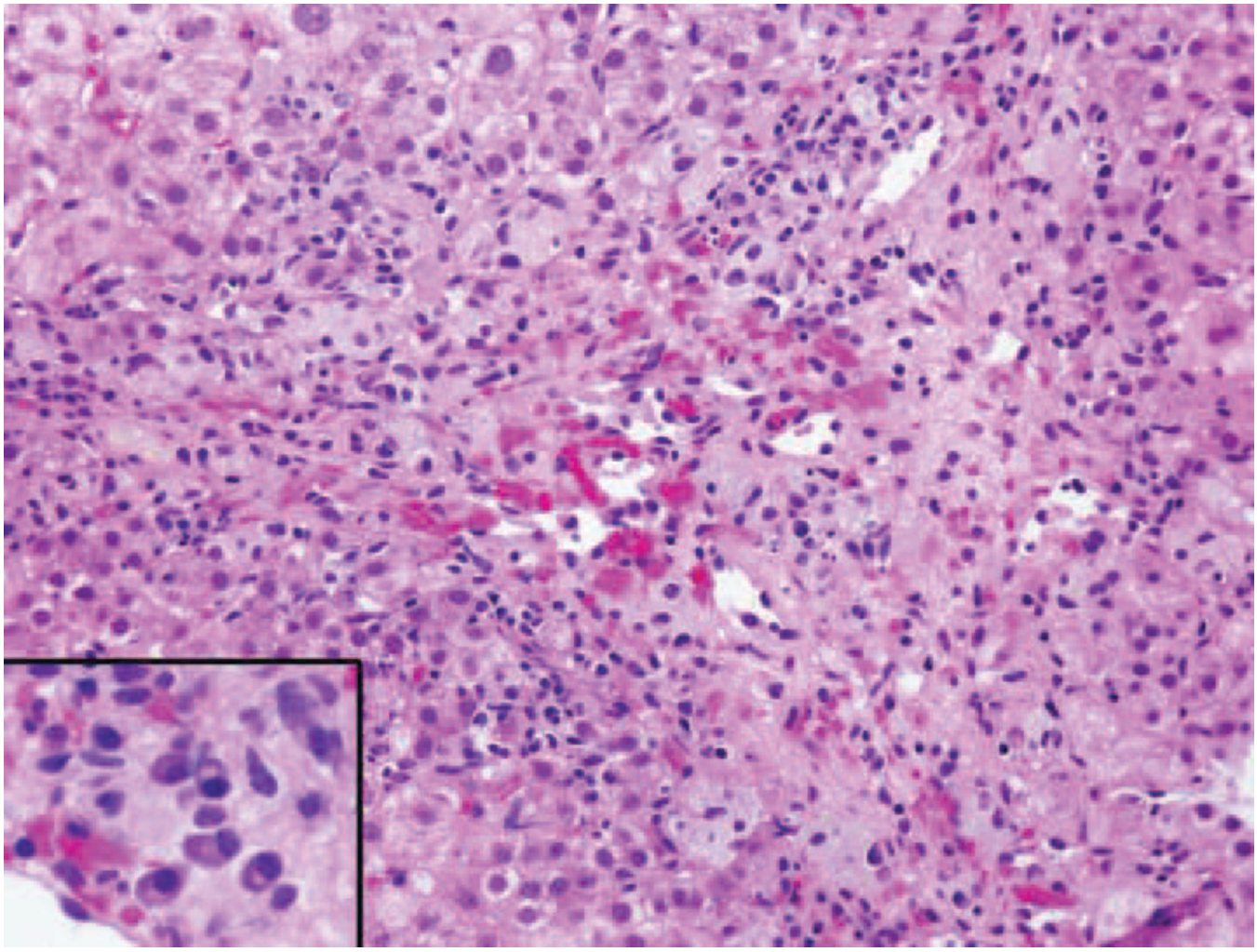

Figure 3. Hepatic histopathology of interferon beta hepatotoxicity

A representative photomicrograph from the liver biopsy of patient #7 shows zone 3 necrosis. There is a sparse infiltrate of lymphocytes and plasma cells, mainly along the edge of viable cells. Pigmented macrophages and mild hemorrhage are also seen. Insert: A cluster of plasma cells from another focus of necrosis (H & E, 400 fold magnification).

Table 1

Clinical features of 8 cases of Interferon Beta Hepatotoxicity in the DILIN Registry

Patient #	Age (yrs)/ gender	Race	BMI (kg/m2)	Product	Latency (days)	Initial ALT (IU/ml)	Initial Alk P (IU/l)	Initial bili (mg/dl)	R	DILIN severity score	DILIN causality	Biopsy (days from DILI onset)	Outcome
#1	42 F	Cau	31.8	Beta 1a IM (Avonex)	175	282	95	0.9	6.7	1	2		Resolved
#2	38 F	Cau	29	Beta 1 b (Betasero n)	633	366	322	0.5	3.2	1	1	Yes-40 days	Positive rechallenge persistent alk phos elevation at 2 years
#3	52 F	Cau	22.3	Beta 1a SC (Rebif)	143	220	74	0.3	10.4	1	2		
#4	62 F	Cau	27.2	Beta 1a SC (Rebif)	1734	240	83	0.4	10.1	1	3		
#5	59 F	Cau	22	Beta 1a SC (Rebif)	1475	1225	220	2.8	12.3	2	2		Ezetimibe-simvastatin considered possible
#6	46 F	Black	40.1	Beta 1a IM (Avonex)	101	850	91	0.7	29.2	2	1	Yes-74 days	
#7	64 F	Cau	21.3	Beta-1a IM (Avonex)	4700	713	349	0.6	4.3	3	4	Yes- 24 days	Oxaprozin considered very likely, 2 week course of prednisone
#8	33 F	Black	47.8	Beta 1a SC (Rebif)	292	1901	224	4.5	23.5	5	1	Yes- 30 days	Given steroids but died of liver failure 77 days after DILI onset
Mean + SD	49 + 9	75% Cau	30.2 +9.5		1156 + 1109	725 + 593	182 + 96	1.3 + 1.2	12.4 + 6.9	1.7 + 1.3	2 + 1.1	41 + 22 days	

Table 2

Published series of Interferon Beta hepatotoxicity

Series (ref)	n	Age/ gender	Race	Product used	Latency (days)	Initial ALT/ Alk/ Bili	R	DILIN severity	Biopsy	Outcome
Durelli (1998) #16	1	24 F	Cau	IFN-B1b8 MUqod	152	100/NA/NA	NA	1	No	+ Autoantibodies. Interferon continued with resolution
Yoshida (2001) #18	1	59 F	Cau	IFN B1a 22 ug tiw	42	1360/165/ 27	26.0	5	Y- massive necrosis	Transplanted 3 days after presentation. Also had received nefazadone
Duchini (2002) #20	1	38 F	Cau	IFN B1a	730	1875/221/18.7	17.8	3	Y- Zone 3 necrosis	+ Autoantibodies Improved with steroids and azathioprine
Wallack (2004) #17	1	52 F	Cau	IFN B1a 8.8 ug tiw	14	NA/NA/ 28.6	NA	2	No	+ Autoantibodies Improved with steroids
Pulicken (2006) #23	1	43 F	NA	IFN-B1a44 ug tiw	42	391/NA/0.5	NA	2	Y-AIH like	+ Autoantibodies Improved with steroids
Byrnes (2006) #19	3	37 F	Cau	IFN B1a 30 ug IM q w	300	1,031/ NA/ 11.9	NA	2	Y-AIH like	+ Autoantibodies Interferon continued with relapse in hepatitis 9 months later. Required steroids & azathioprine Hepatitis with IVIG as well.
		37 F	Cau	IFN-B1a 8.8 ug sq tiw	19	230/ NA/ NA	NA	1	Y-Pericentral necrosis	Improved with steroids
		30 F	Cau	IFN-B1a	63	108/ NA/ NA	NA	1	Y-pericentral	+ Mild autoantibodies

Series (ref)	n	Age/ gender	Race	Product used 44 ug tiw	Latency (days)	Initial ALT/ Alk/ Bili	R	DILIN severity	Biopsy necrosis	Outcome
Grieco et al (2007) #15	1	43 F	Cau	IFN-B22 ug biw	14	995/695/12.5	8.8	3	Yes- Centrilobular necrosis	+ Rechallenge Recovered
Montero (2007) #22	1	39F	NA	IFN-B25 ugsc weekly	1825	1082/176/10.4	16.9	5	Y- massive necrosis	+ Autoantibodies Liver Transplant
Pietrosi G (2008) #21	1	46 F	NA	IFN B1a30 ug q week IM	950	1232/221/15.2	12.8	5	Y- Massive necrosis	Liver Transplant
Mean or %	11	40 + 10.2	100% Cau		386 + 601	840/295/15.6	16.4 + 6.4	2.7 + 1.6		

AIH= Autoimmune hepatitis like with lymphoplasymatic infiltrate Cau= Caucasian NA= Not available